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Pharmacokinetics and biopharmaceutics of some adrenergic beta-receptor antagonists with special emphasis on alprenolol and metoprolol

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CARL-GUNNAR REGÅRDH

GÖTEBORG 1975

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This survey is based on the following papers which are referred to by Roman numerals in the text.

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VII. Regårdh C-G, Johnsson G, Jordö L & Sölvell L: Comparative bioavailability and effect studies on metoprolol administered as ordinary and slow-release tablets in single and multiple doses. Acta Pharmacol Toxicol (Kbh) 36 suppl 5: 45—58, 1975.

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1. GENERAL SURVEY

The finding that the relative potency of a series of sympathomimetic amines varied with the effector organs or systems studied led Ahlquist (5) in 1948 to conclude that there are "two distinct types" of adrenergic receptors. Ahlquist classified them as alpha and beta-receptors. At that time only responses attributed to alpha-receptor activation could be successfully blocked by the known adrenergic receptor antagonists, whereas there was no agent available which inhibited the responses attributed to the beta-receptors. It was to take another ten years until such a compound, a dichloro-analogue of isoprenaline, DCI, was discovered and until then Ahlquist's theories were the subject of a great deal of scepticism. The discovery that DCI selectively blocked responses which according to Ahlquist were mediated by the beta-receptors greatly strengthened the arguments for two major types of adrenergic receptors and the alpha and beta classification has since then come into general use.

Later studies have shown that both alpha and beta-adrenergic receptors are usually present in the same organ but often the effect induced by one or other type of receptor dominates. Alpha-receptor mediated effects are, for instance, contraction of the smooth muscles in the blood vessels, ureter and iris whereas stimulation of the beta-receptors results, for instance, in an increase of the heart rate and contractile force and relaxation of smooth muscles in blood vessels, bronchi, intestine and uterus.

After the discovery of the beta-blocking properties of DCI a great number of other compounds classified as adrenergic beta-receptor antagonists, beta-receptor blockers or simply beta-blockers, have been synthesized, all of them competitively inhibiting the agonistic action of various catecholamines at adrenergic beta-receptor sites. Some of these compounds have, during the last decade, become valuable agents in the treatment of various cardiovascular disorders.

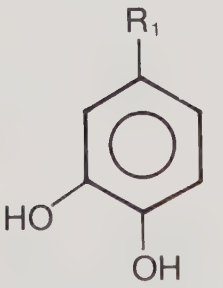
A. *Classification of the beta-receptor antagonists*

Studies by Lands and associates (63) have shown that the beta-receptors in different tissues do not have identical properties. These authors proposed the existence of two types of beta-receptors which they termed $beta_1$ and $beta_2$, the former mediating, for example, cardiac stimulation and the latter relaxation of vascular and bronchial smooth muscles. Support for this classification of the beta-receptors was obtained with the introduction of the beta-receptor antagonist practolol (33) which is 50 to 100 times more active in inhibiting the chronotropic response to isoprenaline than in inhibiting the effect of this agonist on the vascular and tracheal smooth muscles (15). The separation is not absolute as inhibition of vascular and tracheal sites occurs when the concentration of the antagonist is sufficiently high and for this reason drugs with a similar differentiated action on the beta-receptors have been termed "$beta_1$-receptor selective"

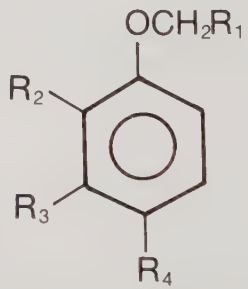
instead of "$beta_1$-receptor specific". Classification of the beta-receptor antagonists according to the relative selectivity for the different types of the beta-receptors, however, does not give a complete characterization of these drugs. In addition, some of them possess an agonistic activity — or intrinsic sympathomimetic activity as it has also been termed. Antagonists with this property have been classified as "competitive dualists" (3) according to the terminology of Ariens and associates (10). The partial agonistic activity of these drugs differs from that of the catecholamines in that the intrinsic activity is lower although the affinity to the receptor sites is often high. Some of the beta-receptor antagonists also have local anaesthetic or membrane stabilizing properties which are manifested as a prolongation of the effective refractory period and a reduction of the height and rate of rise of the action potential.

B. *Beta-receptor antagonists in therapeutic use*

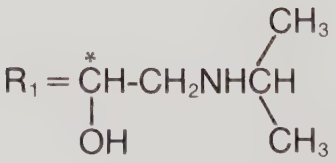
Through DCI, whose beta-receptor blocking activity was described in 1958 (72), a general idea of the molecular structure essential for the antagonistic effect was obtained. DCI was followed by pronethalol (16) in 1962 but for various reasons both of these compounds were rejected before being taken into therapeutic use. Ever since then, numerous compounds classified as beta-receptor antagonists have been described by pharmacologists and chemists. The first ones to gain official approval were propranolol, alprenolol, oxprenolol, pindolol and practolol. All these drugs exhibit a clear structural relationship to isoprenaline, the prototype beta-agonist, as shown by the following formulae:



isoprenaline



beta-receptor antagonist



The high affinity to the beta-receptors appears to be associated with the isopropylamino group in the side-chain of both the agonist and the antagonist. The main structural differences between isoprenaline and the beta-blocking drugs mentioned are found in the catechol ring but also the distance between the amino group and the nucleus is enlarged by interposition of a carbon and an oxygen atom.

Both isoprenaline and the beta-receptor antagonists have an optically active carbon atom in the side-chain (indicated by an asterisk) and therefore exist as pairs of optical isomers. The pharmacological properties of the isomers have been studied in detail for propranolol (14, 43) and to less extent for alprenolol (1) and for both of these drugs the (—) isomer has been found to have 50 to 100 times higher activity than the (+) isomer as competitive inhibitors although both may show other non-stereospecific properties including "quinidine-like" and local anaesthetic activity.

C. *Pharmacodynamic effects*

The beta-receptor antagonists induce a variety of pharmacodynamic effects, the most interesting from a medical point of view being the cardiovascular hemodynamic effects e.g. reduction of heart rate and cardiac output and prolongation of atrioventricular conduction. Owing to these effects the beta-blockers now occupy an essential position in the therapeutic arsenal as valuable agents for angina pectoris, hypertension and arrhythmias.

Other effects that are associated with the administration of beta-blocking drugs are bronchial constriction (66, 67) and various metabolic effects, such as decreased plasma renin activity (25, 29, 84) and a weak hypoglycemic effect (7).

2. AIM OF THE INVESTIGATIONS

The need for a correct understanding of the pharmacodynamic action of a drug is self-evident in modern pharmacotherapy. Successful treatment, however, also requires insight into the pharmacokinetics of the drug, such as the rate and extent of absorption, metabolism and excretion of the compound and the relationship between the body levels of the drug and the pharmacological effects. These properties have been studied to varying extent for the different beta-receptor antagonists. Thus, for some of them e.g. propranolol, alprenolol and practolol, a great deal of human pharmacokinetic data have been reported in recent years whereas surprisingly little information of this kind is yet available for some of the other beta-blockers despite their therapeutic use for several years.

This survey presents the results of pharmacokinetic studies on the beta-receptor antagonists alprenolol and metoprolol. The studies have been carried

out in order to clarify some pharmacokinetic points of vital importance for the design of proper dosage forms and regimens and for the understanding of the relationship between the plasma levels of the two drugs and the beta-receptor blockade determined as the effect on heart rate and arterial blood pressure at rest and during exercise. Pharmacokinetically, however, several points still remain to be elucidated in human beings for both alprenolol and metoprolol and consequently the present investigation makes no claim to give a complete picture of the pharmacokinetic properties of these compounds. Pharmacodynamically, the compounds studied represent two different types of beta-blockers. Thus, alprenolol is classified as a non-selective beta-blocker with intrinsic sympathomimetic activity whereas metoprolol is the first described cardioselective beta-receptor antagonist devoid of intrinsic activity (3). Pharmacokinetic data on other beta-blockers, available in the literature, have been included in the text in order to facilitate comparison between the pharmacokinetic properties of alprenolol and metoprolol and those of other drugs belonging to the same group.

3. METHODS USED IN THE INVESTIGATIONS

A. *Materials and design of the studies*

The studies have mainly been carried out in healthy volunteers (I—V, VII) but in one study (VI) patients with mild hypertension were used. Age, sex and body weight are reported separately in each paper. All subjects had normal kidney and liver function according to routine laboratory tests (serum creatinine, bilirubin, SGPT and SGOT). Before the experiments started written information about the purpose of the study and the experimental design was given to each of the subjects. In the studies with radioactive alprenolol and metoprolol permission to use the tritiated drugs was given by the Isotope Committee of Sahlgrenska Hospital, Göteborg.

The experimental design of the studies has been adapted to the specific questions intended to be clarified. As a general rule, however, the subjects fasted for about twelve hours before the commencement of the study and food was thereafter withheld for an additional 3—4 hours irrespective of whether the drug was administered orally or parenterally.

B. *Variables estimated*

The variables that have been studied include the plasma concentration of the parent drugs and metabolites, urinary excretion of these compounds and the pharmacodynamic effects recorded as the reduction of exercise and resting heart rate and arterial blood pressure.

The analyses of the parent drugs have been carried out by selective gas

chromatographic methods including derivatization to EC-detector sensitive compounds (34, 35) in the studies with cold drug. When tritium-labelled drug was administered radiometric methods were applied. These methods gave virtually the same plasma concentrations of unchanged drug as the gas chromatographic ones (I, IV, VII) but substantially higher concentrations in the urine due to co-determination of some metabolite(s) (II, IV).

Total metabolites have only been determined after administration of the tritium-labelled compounds by measuring the total radioactivity in plasma, serum and urine. 4-OH-alprenolol, which is the main metabolite of alprenolol, was determined by ion pair partition chromatography as described by Borg et al. (20).

The effects on the exercise heart rate and arterial blood pressure have been studied at sub-maximal work load on an electrically braked ergometer bicycle adjusted to give a pulse rate of about 150 beats per minute in each individual before medication. Each exercise period lasted for five minutes and during the test the heart rate was recorded continuously by an Offner tachometer. The tests were performed at fixed intervals of 90 minutes. With this test frequency the effect of the preceding test did not significantly influence the result of the next exercise test as indicated by the almost constant heart rates during the placebo experiments in most of the studies. The arterial blood pressure was measured by the conventional auscultatory method during the last minute of exercise. At that time the heart rate had generally reached a constant level. The resting values of the heart rate and blood pressure were registered in the recumbent position immediately before each exercise period. Due to technical reasons, only the systolic blood pressure was recorded during exercise. At rest the diastolic blood pressue was registered as Korotkoff V.

C. *Determination of in vitro dissolution and disintegration rates*

In two of the studies (I, VII) tablets with different dissolution rates have been administered to test the effect of the dissolution rate on the extent of bioavailability and duration of action of the drug. The dissolution rates of the slow-release preparations were determined according to a slightly modified Levy and Hayes beaker method (I) whereas conventional tablets of alprenolol were tested with respect to the disintegration time according to the British Pharmacopoeia of 1968, and the dissolution rate of the metoprolol tablet was determined by the rotating basket method of the United States Pharmacopeia Ed. XVIII.

D. *Calculations*

Generally the results are presented as mean values and s.e.m. but individual data are occasionally given in tabular form in order to stress the interindividual variation of the results. Tests of the significance level of differences between obtained results have been carried out using Student's t-tests for paired and

unpaired observations. Statistical significance has been defined as $p < 0.05$.

Numerical integration by the method of overlapping parabolas (32) has consistently been applied for determination of the areas under the plasma concentration curves (AUC) during the time of the experiments, as this method in our experience, gives a somewhat greater precision to the results than the commonly used trapezoidal rule. The rest areas, i.e. the AUC between the last time of sampling and infinity, have been determined by the method of Wagner (87). This method is, however, only applicable provided that the last plasma sample is collected in the monoexponential phase, which has consistently been the case in the studies included in the present dissertation.

Regression analysis of linear and non-linear functions has been carried out by the methods of least squares using various types of computer programmes. Calculations of confidence limits and levels of significance of the various constants associated with linear regression were carried out according to Woolf (89). Non-linear regression analysis has been carried out by programmes based on the Gauss-Newton procedure. The programmes used were DECUS No. 8—661 (Fortran IV programme for Digital PDP 8 computer) and a revised version of the BMDX 85 programme which was run on an IBM 360/75 digital computer.

4. ABSORPTION AND BIOLOGICAL AVAILABILITY OF ORALLY ADMINISTERED ALPRENOLOL AND METOPROLOL

The secondary amino group in the side-chain characteristic of the beta-receptor antagonists gives all these drugs weak basic properties. The pK_a of the corresponding acids are about 9.7. As bases the drugs are slightly soluble in water but the solubility can be substantially increased by salt formation with various inorganic and organic acids, e.g. hydrochloric, sulphuric and tartaric acid. Among the commercially available beta-blockers, alprenolol, propranolol, oxprenolol and sotalol are used as the hydrochlorides whereas pindolol and practolol are administered as the bases. Due to the value of the dissociation constant of the amino group, however, all the beta-blockers exist predominantly in ionized form at the physiological pH values of the alimentary canal and, consequently, all of the beta-blockers mentioned dissolve rapidly in both gastric and intestinal juice. This is also the case for the new beta-blocker metoprolol which was administered as the neutral tartrate.

A. *Rate of absorption*

Normally, highly water-soluble drugs, that are absorbed by passive diffusion

through the gastrointestinal mucosa, are rapidly absorbed when administered in rapidly dissolving pharmaceutical formulations. In this respect the beta-receptor antagonists form no exceptions. A number of studies with drugs belonging to this group (I—VII and e.g. 17, 19, 51, 62, 70, 73, 74, 86) indicate that oral doses of these compounds rapidly pass through the gastrointestinal barrier. This information is primarily based on the time taken to reach the maximum plasma concentration which usually occurs within 1—2 hours after administration of conventional tablets. Attempts to determine the rate of absorption seem only to have been made for metoprolol (IV) and pindolol (51). Assuming that the absorption process follows first-order kinetics, which admittedly might be a great over-simplification, the half-life of the absorption of metoprolol was 12 minutes (IV) administered as a slightly acidic solution. For pindolol, which was given as a conventional tablet, the corresponding value was close to 18 minutes (51). The difference is probably due to the dissolution step involved in the absorption process of pindolol.

When metoprolol was administered in solution, 10 minutes elapsed on average between the time of administration and the appearance of the drug in the systemic circulation. This time, commonly named the *lag time*, conceivably reflects the time for the drug to reach the small intestine as the absorption from the stomach is probably insignificant, as indicated by buccal absorption studies on solutions with pH values less than 4 (unpublished observations).

As probably all the beta-receptor antagonists are absorbed from the alimentary canal at approximately the same rate as metoprolol when administered as solutions, the rate of absorption of these highly water-soluble drugs is affected by the rate of dissolution from the pharmaceutical formulation. Thus, by changing the dissolution rate of the drug from the oral preparation the rate of absorption and the plasma concentrations can be adjusted to proper levels. This approach has been applied to alprenolol and metoprolol, which were administered in slow-release tablets of the insoluble matrix type* (I, VII). In both studies the rate of dissolution significantly influenced the absorption rate of the drugs, which resulted in lower peak plasma concentrations and changes of the time-courses of the plasma concentration curves in comparison with those of conventional tablets. For both of the compounds the rate of absorption was almost identical to the in vitro dissolution rate from the slow-release tablets, which is characteristic of the type of slow-release tablets used.

B. *Extent of absorption*

Studies by Harris and Riegelman (53) and by Barr (13), among others, have shown that complete uptake of a drug from the gastrointestinal tract does not automatically imply that the entire dose is systemically available. Conse-

* Durules®, AB Hässle

quently, it is essential to draw a distinction between the fraction of the dose passing through the intestinal barrier as unchanged and as metabolized drug — in this survey termed the extent of absorption — and the fraction of the dose ultimately reaching the systemic circulation in unchanged form. The latter is in this context referred to as the extent of bioavailability according to the terminology of APhA, Academy of Pharmaceutical Sciences (8).

The extent of absorption of alprenolol and metoprolol administered in solution, conventional tablets and in slow-release form* has been determined from the urinary recovery of total radioactivity during 72 hours after administration of tritium-labelled doses of the drugs (I, IV, VII). Irrespective of the type of formulation, the mean urinary excretion of radioactivity reached more than 90 per cent of the administered dose in all these studies indicating that both drugs are completely absorbed from the alimentary canal and that the absorption takes place over a large part of the intestine as the radioactive doses were almost completely recovered even with the slow-release tablets. High urinary recoveries in human beings have also been reported for oxprenolol (74), pindolol (51), practolol (17, 28, 40) and propranolol (86), which indicates that all beta-receptor antagonists presently available for medical use are well absorbed from the intestine.

C. *Extent of bioavailability*

Despite the beta-receptor antagonists being well absorbed from the alimentary canal, the extent of bioavailability of these drugs varies considerably. Thus, propranolol undergoes extensive biotransformation during the initial transfer from the intestinal lumen into the general circulation (80). Others, e.g. pindolol and practolol, appear to be completely systemically available after oral administration (17, 28, 51). Oxprenolol seems to occupy an intermediate position with respect to the presystemic elimination as suggested by the data from a study with a single 20 mg dose in four volunteers (74).

Like propranolol, alprenolol is extensively metabolized during the first passage through the gastrointestinal mucosa and the liver. It is shown in paper III that on average about 7 per cent of an oral 100 mg dose of alprenolol is systemically available. About the same value has recently been obtained by Perrier et al. (71) and by von Bahr et al. (12). In the latter study the bioavailability varied between 1 and 16 per cent in six subjects. The reported average values are in good agreement with the observed 10:1 ratio between the equipotent oral and intravenous doses of the drug (58). Metoprolol, on the other hand, has an average bioavailability of about 45 per cent for oral 50 mg and 100 mg doses (V).

The extent of bioavailability of the beta-receptor antagonists appears primarily to be related to the hepatic clearance of the compounds (III, IV, 12, 71,

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81) so that low hepatic clearance results in high systemic availability and vice versa. For alprenolol and propranolol, having the greatest "first-pass" elimination, the extent of bioavailability is dose-dependent and a progressively higher fraction of the dose reaches the systemic circulation as the dose is increased (2, 81). The data presented in paper I further indicate that the rate of absorption of these compounds might influence the extent of bioavailability as the AUC and the urinary recovery of unchanged alprenolol were decreased when the absorption rate was reduced by administration of the drug in slow-release tablets. The reduction of the availability, however, was not great enough to imply that sustained-release administration of alprenolol is unsuitable, particularly as alprenolol in slow-release form has been found favourably to influence the duration of action of this drug (60).

A possible explanation for the dose and absorption-rate-dependent bioavailability of beta-blockers with low bioavailability has been provided by Evans and associates (39). On the basis of animal data, these authors have proposed that propranolol is extracted by the liver by two separate systems — one with high affinity but low capacity for the drug and another with lower affinity but of much larger capacity. The mechanism of low capacity is already saturated at low dose levels and according to Evans and Shand (36) it remains saturated throughout a dosage interval of six hours, leading to higher bioavailability of all doses subsequent to the first one. In a study on the hepatic removal of alprenolol in the rat, Grundin et al. (50) have recently proposed that the high affinity binding site might be the microsomal cytochrome P-450 system.

An estimation of the relative capacity of the high affinity binding sites of the liver for various beta-blockers might be obtained from the apparent threshold value of oral doses of these drugs, i.e. the minimum dose required to give detectable plasma concentrations. For metoprolol the threshold value is 8 mg whereas for metoprolol the corresponding value is 31 mg, indicating that the capacity of the rapidly eliminating system is considerably lower for metoprolol than for propranolol. Due to this, the bioavailability of metoprolol seems to be independent of the number of the dose (VI) and also unaffected by the rate of absorption as approximately the same bioavailability was obtained with conventional and slow-release tablets in paper VII.

In addition to the dose and the rate of absorption, the hepatic blood flow and the hepatic extraction ratio for the drug in the systemic circulation influence the extent of bioavailability of the beta-blockers (III, V, 37). The rate of absorption, particularly, might vary substantially inter and intraindividually at a fixed dose but even the liver blood flow varies twofold between different individuals. These variations result in great interindividual disparities between the plasma concentrations of unchanged drug at constant dose levels. The variations are especially great for alprenolol and propranolol, which have the most efficient hepatic removal of the beta-blockers and for these compounds twenty—twenty-fivefold variations between the steady state plasma levels in different individ-

uals have been reported (73, 82). For the systemically more completely available metoprolol the plasma levels fluctuate significantly less between different individuals both after an acute dose and at steady state. In the studies presented in paper VI and VII there was at most a sevenfold variation between the bioavailability among the twenty subjects included in these studies.

5. TISSUE DISTRIBUTION AND PROTEIN BINDING

After intravenous administration of various beta-receptor antagonists the plasma concentrations of the parent drugs decline biphasically and the pharmacokinetics of the drugs are adequately described by the two-compartment model. The initial rapid phase (alpha-phase) describes the distribution of the drugs to tissues represented by the so-called peripheral compartment and the slowly declining phase (beta-phase) reflects the elimination of the drug from the total body after establishment of pseudo-distribution equilibrium.

A. *Rate of distribution*

The plasma concentration curves of intravenously administered alprenolol and metoprolol (III, IV) show that the alpha-phase has on average ceased within one hour after the injection of these drugs. The mean half-life of the distribution process of metoprolol has been calculated to be 0.20 ± 0.05 hours (range 0.09—0.33 hours, IV). Similar half-life values have been reported for the distribution of other beta-blockers e.g. propranolol (80) and practolol (4). The alprenolol data presented in paper III further indicate that even this drug is rapidly distributed in the body, the half-life being about the same as for the other compounds mentioned.

B. *Volume of distribution*

In addition to the distribution half-life, which merely gives information about the time required to reach pseudo-distribution equilibrium, it is also essential to know the volume of distribution of the drug as this constant is directly proportional to the clearance of the drug (78) and relates the plasma concentration to the total amount of drug in the body. For the beta-receptor antagonists in general the total volume of distribution is larger than the physiological body space, which indicates that this type of drugs cumulates in certain extravascular sites. This has also been confirmed by animal studies (19, 54, 79) which have shown that the concentrations of the beta-blockers are substantially higher in tissues e.g. heart, lungs and liver, than in the plasma.

From the average AUC presented in paper III, the mean distribution volume

of alprenolol at pseudo-distribution equilibrium, $V_{d, \beta}$, can be estimated to be 3.3 l/kg body weight by the method of Gibaldi et al. (45). The values are based on an average body weight of 70 kg and are in good agreement with the recently reported value of 3.0 l/kg body weight by Bodin et al. (19). A still more extensive tissue distribution has been found for metoprolol (IV). For this drug $V_{d, \beta}$, was 5.6 $\pm$ 0.2 l/kg body weight and about 40 per cent of this value, or 2.2 $\pm$ 0.3 l/kg body weight was due to the volume of the so-called central compartment of the two-compartment model. The relatively high apparent volume of the central compartment indicates that the drug in the plasma rapidly equilibrates with highly perfused organs which constitute the major volume of the compartment.

C. *Factors affecting the volume of distribution*

The apparent mean body space of alprenolol is about the same as reported for propranolol by Evans et al. (38). These compounds seem to represent a medium group with respect to the distribution volume of the beta-receptor antagonists. Lower values have, for instance, been found for pindolol, 2.0 l/kg body weight (51), and practolol, 1.6 l/kg body weight (17), whereas metoprolol has the most extensive tissue distribution of the beta-blockers reported so far. The reasons for the different extent of tissue distribution of these drugs are probably to be found in the differences in lipid solubility and protein binding between the drugs as these factors, in addition to the regional blood flow, are in general considered to be the most important for the tissue distribution of various organic compounds. Thus, Evans et al. (38) recently showed that $V_{d, \beta}$ of propranolol increased when the fraction of unbound drug in the blood and plasma was raised and a similar relationship probably exists between $V_{d, \beta}$ of the various beta-blockers and the protein binding of these compounds. Another recent study, by Keberle et al. (61) on a series of sulphonamides has shown a clear-cut relationship between the lipid solubility of these drugs and their tissue distribution so that the latter increased with increasing lipophilicity of the compound. Alprenolol and propranolol are bound to human serum proteins to approximately 85 and 93 per cent respectively (37, 57) and they also have about the same polarity, as indicated by the partition coefficients between the octanol/water system which are 3.27 and 5.39 respectively at pH = 7.0 (55). According to Johansson et al. (57), the fraction of metoprolol bound to serum proteins is only 11 per cent and the partition coefficient is 20—30 times lower than for the two former compounds. The lower degree of protein binding favours the tissue distribution of the drug whereas the lower lipid solubility has the opposite effect but apparently the protein binding is the dominating factor for the tissue distribution of metoprolol. The same might also be valid for the other beta-blockers (e.g. pindolol and practolol) but at present there are no conclusive data available as different methods have been used in the assessment of the protein binding of these two drugs (49, 51) and of the other three.

6. ELIMINATION OF THE PARENT DRUGS

As previously mentioned, a relatively large fraction of oral doses of some of the beta-receptor antagonists is lost during the initial transport from the gastrointestinal lumen into the general circulation by mechanisms that are generally referred to as the "first-pass" effect or pre-systemic elimination. This concept has already been discussed to some extent in connection with the biological availability of the beta-blockers and has therefore been omitted in the following paragraphs. These concentrate instead on the routes and particularly the rates of elimination of alprenolol and metoprolol as the elimination studies included in this survey mainly concern the rates of these processes and the effect of various factors, for instance chronic administration and the dose administered, on these processes.

A. *Routes of elimination*

Renal excretion

After oral administration of therapeutic doses of alprenolol insignificant amounts of the parent drug are excreted in the urine (I, II). Assayed by the selective gas chromatographic method of Ervik (34) the urinary recovery of an oral 100 mg dose was ≤ 0.1 per cent in four healthy subjects (II). Metoprolol is excreted in unchanged form in the urine to a somewhat greater extent than alprenolol and after oral administration of subtherapeutic and therapeutic doses 3—5 per cent of the parent drug is recovered in the urine during 72 hours (IV, VII). The recovery is, however, dependent on the route of administration and intravenously administered metoprolol is excreted to about 10 per cent as unchanged drug during the same period (IV). The corresponding value for alprenolol after intravenous administration was 1—2 per cent (unpublished observations).

The urinary recoveries of unchanged alprenolol and metoprolol are in the same range as for propranolol and oxprenolol (74, 86). According to Bodem and Chidsey (17), practolol is eliminated almost completely by renal mechanisms, predominantly glomerular filtration, whereas pindolol is excreted in the urine to about 40 per cent as unchanged drug (51, 69).

Biotransformation

Despite only minor fractions of alprenolol and metoprolol being excreted in unchanged form via the kidneys, more than 90 per cent of the radioactivity administered as alprenolol-(^{3}H) and metoprolol-(^{3}H) is recovered in the urine within 72 hours (I, IV, VII), indicating that the drugs are almost entirely eliminated from the body by biotransformation. The data presented in papers III and IV indicate that both of the drugs are subject to virtually complete hepatic metabolism as the total body clearance of alprenolol, determined from

the AUC after intravenous administration, is only slightly lower than the hepatic blood flow determined according to Perrier et al. (71) and the hepatic blood flow determined from the blood concentration levels of metoprolol (IV) is practically identical with the reported mean value of 1.51 l/min (22).

The major metabolites of both drugs have been identified (II, 18, 21) and some of them have been found to possess an antagonistic effect on the beta-receptors of the cat heart (21, 26). So far, however, only 4-OH-alprenolol, which is the major metabolite of alprenolol, has been shown to be active in man (III) and the potency of this compound appears to be comparable to that of the parent drug.

B. *Rate of elimination*

Urinary excretion rate and renal clearance

Both alprenolol and metoprolol are excreted via the kidneys at a rate that is directly proportional to the plasma concentration of the unchanged compound. The renal clearance value of metoprolol calculated from the slope of the regression line for the relationship between the urinary excretion rate and the plasma concentration was 109 ml/min after correction for protein bound drug (IV). This value is close to the clearance of inulin, indicating that the drug is mainly excreted via glomerular filtration. In the case of alprenolol there is only indirect evidence of a linear relationship between the urinary excretion rate of the drug and the plasma concentration. According to paper II the urinary excretion rate of orally administered alprenolol declines mono-exponentially against time in the post-absorptive phase at a rate that is approximately the same as for the plasma concentration of the parent drug in paper I, indicating that the rate of excretion of alprenolol via the kidneys is directly proportional to the plasma concentration of the drug.

The other beta-receptor antagonists previously mentioned are probably also excreted via the kidneys at a rate directly proportional to the plasma concentration of unchanged drug although conclusive evidence of this has apparently not yet been published. Bodem and Chidsey (17) obtained an average clearance value of 137 ml/min for practolol in five subjects. The corresponding value for pindolol is 216 ml/min according to Gugler et al. (51). It seems, however, that both of these values have been determined without correcting for the fraction of protein bound drug in the plasma, which means that the actual clearance values might be substantially higher.

Total body clearance and elimination half-life ($t_{\frac{1}{2}}$)

The rate of elimination of a drug from the body has until recently almost exclusively been described by the "overall" elimination rate constant or by the half-life. During the last few years, however, the concept of total body clearance has begun to be frequently used as a measure of the elimination rate. Total body

clearance is defined as the volume of whole blood completely cleared of drug per unit time and is a measure of the efficiency of one or several organs in removing the drug. The clearance can be assessed by various methods which have been reviewed by Rowland and associates (77, 78).

The total body clearance of alprenolol and metoprolol has not been explicitly determined so far. Based on the plasma levels after intravenous doses of alprenolol and metoprolol a total body clearance of 0.88 l/min has been obtained for alprenolol and the corresponding value of metoprolol is 1.1 l/min. In the latter case the partition ratio between blood and plasma of 1.2:1 (IV) has been included in the calculations whereas the value for alprenolol has to be adjusted by this factor in order to give the correct value for the body clearance of this drug. As previously mentioned, about 10 per cent of the clearance value of metoprolol is due to renal excretion and the fraction remaining probably reflects hepatic metabolism. For alprenolol practically the whole dose seems to be eliminated via biotransformation in the liver.

Although the clearance concept, which expresses the efficiency of the eliminating organs by taking into account the blood flow and the extraction ratio of the organs, has a great potential in, for instance, predicting the bioavailability and steady state plasma levels, total body clearance is impractical as a measure of the elimination rate of a drug from the blood or from the whole body. The reason for this is that various drugs can have identical clearance and yet be removed at quite different rates due to different volumes of distribution. In discussing the rate of decline of drug levels in the body and the duration of action of various drugs these parameters should therefore preferably be related to the elimination half-life of the drug in the beta-phase.

The average elimination half-life of alprenolol in healthy volunteers varies between two and three hours in the papers included in this survey and similar values have been reported in other studies (2, 19). The value varies comparatively little between different individuals, as is shown by the narrow range of 1.8—2.2 hours for the nine subjects who participated in studies I and II. Metoprolol is eliminated from the body at a somewhat lower rate and the mean values of $t_{1/2}$ obtained in different groups of subjects vary between three and four hours (IV—VII).

The half-life of alprenolol is about the same as for propranolol (70, 80) and oxprenolol (74) whereas the somewhat longer $t_{1/2}$ of metoprolol is more comparable with that of pindolol (51). The total body clearance of the latter drug is, according to Shand (82), about 0.4 l/min, but because of the small volume of distribution the drug is none the less rapidly eliminated from the body. With respect to the elimination half-life, however, one of the beta-blockers, viz. practolol, differs significantly from the other compounds. For practolol the total body clearance approaches the renal clearance (17) and its mean $t_{1/2}$ is therefore substantially longer than for the other beta-receptor antagonists mentioned — reported mean values range between 6 and 13 hours (62, 17).

C. *Various factors that might affect the elimination half-life*

Dose

In recent years it has been shown that a number of drugs are eliminated at a lower rate when the amount of drug in the body is increased. The most well-known example of this is salicylate. For this drug $t_{1/2}$ increases at higher dose levels due to capacity-limited biotransformation. Similarly, the $t_{1/2}$ of, for example, phenylbutazone and diphenylhydantoin vary with the dose but for these drugs mechanisms other than enzyme saturation might cause the prolongation of the elimination half-life.

As regards the beta-receptor antagonists, very limited information has been published about the rate of elimination of various doses. Thus, no systematic evaluation of the relationship between the dose and the elimination half-life seems to have been published as yet. From the data presented by Shand and associates (80) and by Fitzgerald and Scales (40) it seems, however, that at therapeutic levels the dose does not significantly influence the elimination rate of propranolol and practolol. Similarly, the elimination half-life of alprenolol appears to be dose-independent as Åblad et al. (2) obtained almost identical $t_{1/2}$ after oral doses of 50 mg, 100 mg and 200 mg.

The recently completed study on the elimination rate of metoprolol (V) appears, however, to be the most comprehensive study so far of the effect of the dose on the elimination half-life of beta-blockers. In this study four intravenous and three oral doses ranging from 5 mg to 20 mg and from 20 mg to 100 mg respectively were given crossover to five subjects. The elimination half-life determined from the beta-phase was virtually the same after all seven doses, indicating that at sub-therapeutic and therapeutic dose levels the dose does not affect the elimination rate of metoprolol.

Repeated administration

In recent years it also has become evident that not only the dose but also the number of doses and the frequency of administration influence the elimination rate of a number of drugs. The reason for this varies from one drug to another but mechanisms such as enzyme induction and drug cumulation beyond the capacity of eliminating enzyme systems might, for instance, give rise to alterations of the half-life during multiple administration.

Enzyme induction, which leads to a shortening of $t_{1/2}$ during chronic administration, has not yet been reported for any of the beta-receptor antagonists. Instead, it was reported by Evans and Shand (36) that $t_{1/2}$ increased by 44 per cent when 80 mg of propranolol was administered every six hours for two days. According to these authors, this increase of the half-life was probably due to a cumulative effect resulting in sufficiently high body levels to partially saturate the enzyme systems during steady state conditions.

It seems, however, that the study mentioned is the only one in which multiple administration has been found to affect the elimination rate of beta-blockers,

which admittedly might be due to the fact that this question has not been specifically studied for the majority of the beta-blockers. As regards metoprolol, however, the elimination half-life has been determined in 14 female patients with mild hypertension after a single dose of 50 mg or 80 mg and after long-term treatment for at least three months when the patients received the same dose on a t.i.d. regimen (VI). Almost the same $t_{1/2}$ was obtained after the single dose as after three months of metoprolol treatment. Similarly, administration of 100 mg of metoprolol b.i.d. for four days to six healthy volunteers did not significantly influence the elimination half-life of the drug (VII).

The insignificant effect of the strength of the dose and number of doses administered on the elimination half-life of metoprolol reduces the risk of attaining unpredictably high body levels of this drug during chronic therapy. In this respect the pharmacokinetics of metoprolol differ essentially from those of propranolol. The effect of these two parameters on the pharmacokinetics of the other beta-blockers, including alprenolol, remains to be further elucidated.

Drug interaction

When treatment with beta-blockers is indicated the patient often has to continue with this therapy for a long period of his life. Consequently, beta-blockers will frequently be administered together with drugs which might interact with the beta-blockers in one way or another, and it is also quite possible that the beta-blockers in some way affect the pharmacodynamics or the pharmacokinetics of other drugs taken by the patients. Both of these aspects have been investigated to very little extent. The investigation of the effect of concomitant administration of sodium salicylate on the beta-blockade and plasma levels of alprenolol, presented in paper II, appears to be one of the few studies specifically designed to evaluate potential interactions between beta-receptor antagonists and other drugs. Salicylate was chosen because this drug is, to some extent, eliminated via capacity-limited glucuronide formation (65) and preliminary studies had indicated that orally administered alprenolol was eliminated to about 10 per cent as glucuronide. No detectable effect of salicylate on the activity of alprenolol or on the plasma levels and the elimination rate of this drug was, however, observed, indicating that different enzyme systems are involved in the glucuronidation of alprenolol and salicylate.

Alprenolol did not significantly influence the plasma levels or the elimination rate of salicylate although such an effect was considered quite possible as it was anticipated that the beta-blocker would interact hemodynamically with the elimination of salicylate due to changes in the hepatic blood flow. This kind of interaction has, for instance, been reported between propranolol and lignocaine and between propranolol and oxyphenbutazone in the dog (23, 24). Recently, reduced hepatotoxicity of paracetanol in combination with propranolol in mice has been attributed to reduction of liver blood flow after propranolol (11). Whether concomitantly administered beta-blockers also influence the disposition of other drugs in man, for instance by changing the hepatic blood flow, remains to be elucidated.

7. METABOLITE CONCENTRATION IN PLASMA AND ELIMINATION OF METABOLITES

The main metabolites of both alprenolol and metoprolol have, as previously mentioned, been identified and quantitatively estimated in man (II, 18, 21). The pharmacokinetics of two of these metabolites viz. alprenolol glucuronide and 4-OH-alprenolol, have also been studied to some extent (II, III) but so far most of the pharmacokinetic studies in this field have been carried out with the pooled metabolites after administration of alprenolol-(^{3}H) and metoprolol-(^{3}H) respectively (I, IV).

For both of these compounds the pooled metabolites are recovered in the plasma in concentrations considerably exceeding those of unchanged drug. Thus, after oral administration of 100 mg of alprenolol hydrochloride the concentration of radioactive metabolites, calculated as alprenolol, was about one hundred times greater than for the parent drug (I). Similarly, the plasma levels of total radioactive metabolites were on average about twentyfive times higher than for unchanged metoprolol after oral administration of 5 mg of the drug (IV). The ratio between the concentration of the metabolites and the parent drug is, however, dependent on the route of administration and after intravenous administration of 5 mg of metoprolol tartrate the plasma levels of the pooled metabolites are only about ten times higher than for the unchanged drug (IV). The effect of the route of administration on the relationship between the concentrations of the metabolites and the parent drug is still more pronounced for alprenolol, as shown by the 10:1 and 1:1 ratio between alprenolol and 4-OH-alprenolol after intravenous and oral administration respectively (III).

After oral administration of alprenolol and metoprolol the logarithm of the plasma concentrations of the unchanged drug and of the pooled metabolites declined linearly against time in the post-absorptive phase (I, IV). The lines have virtually the same slopes, indicating that the parent drugs and their metabolites have identical half-lives in man. Half-lives apparently identical to that of alprenolol have also been obtained for the isolated metabolites alprenolol glucuronide and 4-OH-alprenolol after oral and intravenous administration of the parent drug, i.e. when the metabolites are formed in the body. Presumably, however, the apparently identical half-lives are the effect of a much more rapid elimination of all of the metabolites than of the parent drug as in such a situation the terminal phase of the logarithmic plasma concentration curve for each of the metabolites, as well as for the pooled metabolites, will reflect the rate of removal of the parent drug from the body. For alprenolol and metoprolol this rate is virtually the same as the formation rate of the metabolites.

Support for the hypothesis that the metabolites of alprenolol are eliminated much faster than they are formed was obtained after parenteral administration of the major metabolite 4-OH-alprenolol. Omitting the formation step by

intravenous administration of the metabolite resulted in a much faster decline of the plasma levels of the metabolite than after intravenous and oral administration of the parent drug (III). The half-life of the disappearance of 4-OH-alprenolol from the plasma was only about 20 minutes after intravenous administration of the compound, which was about ten times shorter than the estimated half-life of the same metabolite after administration of alprenolol (III).

The apparently identical elimination half-lives of metoprolol and its pooled metabolites (3.0 hours) were only obtained after oral administration. When the drug was instead given intravenously the total metabolites were eliminated at a lower rate than the parent drug, the half-lives being 5.0 and 3.0 hours respectively (IV). The longer elimination half-life of the metabolites after intravenous administration of the drug than after oral administration might depend on various factors. Potentially, the drug is metabolized by different pathways after oral and intravenous administration or the metabolites are distributed into deeper compartments after parenteral administration. Further studies are, however, required to give a more definite answer to this point.

A longer half-life of the pooled metabolites than of the parent drug has also been reported after intravenous administration of propranolol (70), whereas after oral administration the half-lives seem to be approximately the same (70, 86). For propranolol, too, the plasma levels of the total metabolites are considerably higher than for the parent drug, the peak plasma levels of the metabolites being 25—100 times higher than for unchanged propranolol after oral administration (70).

Compared to the high ratios between the plasma levels of the pooled metabolites and of alprenolol, metoprolol, and propranolol, the approximately 5:1 ratio between oxprenolol metabolites and oxprenolol reported by Riess et al. (74) seems unexpectedly low, especially as this compound also is mainly eliminated by biotransformation, with a half-life of about two hours. The comparatively low plasma levels of the total metabolites of oxprenolol might be due to very rapid excretion or extensive extravascular distribution of the metabolites.

8. INDIVIDUAL VARIATION OF THE PLASMA LEVELS OF THE BETA-RECEPTOR ANTAGONISTS

Pharmacokinetic studies have shown that the plasma concentrations of several drugs vary substantially between different individuals receiving the same amount of drug. The largest variation is generally observed when a drug is given orally, whereas the plasma levels fluctuate to much less extent after intravenous administration. In the latter case the variation in the plasma levels is mainly due to interindividual disparities in the volume of distribution and in the elimination capacity of systemically available drug. After oral administra-

tion two further factors viz. absorption from the gastrointestinal tract and pre-systemic elimination, might influence the plasma levels. The latter factor is particularly important for drugs with a relatively large first-pass effect (76) and, as mentioned previously, some of the beta-blockers, including alprenolol, belong to this category. On the other hand, most of these drugs are completely absorbed from the gut (I, IV, 17, 51, 70, 74). In papers I and II the peak plasma levels of alprenolol varied ten to twentyfold after an acute dose of 100 mg of the drug. About the same variation between the peak plasma levels of alprenolol in different individuals has been reported by Åblad et al. (2) and by Bodin et al. (19). In the latter study it was also shown that the plasma concentrations of unchanged drug varied to much less extent after intravenous administration, indicating that the large interindividual variations in the plasma concentrations of alprenolol after oral administration are primarily due to varying pre-systemic elimination.

The variation of the maximum concentration of alprenolol in the plasma discussed above has been observed after an acute dose but it has recently been shown that the mean plasma levels vary to about the same extent after multiple administration to steady state (73).

Large interindividual differences in the plasma concentrations have also been reported for propranolol and, according to Shand (82), the variation seems to be of the same magnitude as for alprenolol. According to available data, the plasma concentrations of these two beta-blockers appear to differ more inter-individually than those of the other drugs of the same group, with the possible exception of oxprenolol. For this drug a sixfold difference in the plasma levels has been observed in four subjects (74) but potentially the variation would have been still greater in a larger number of subjects. For pindolol only a fourfold interindividual variation of the plasma concentrations has been reported (51), which agrees with the high bioavailability of this compound (51). Small variations have also been reported for practolol and for this drug the intraindividual variation seems to be larger than the variation between different subjects (28).

As regards metoprolol, individual plasma data from 20 subjects receiving single and multiple doses have been presented in papers VI and VII. At the three dose levels used (50, 80 and 100 mg of metoprolol tartrate) the peak plasma levels varied at most sevenfold both after a single dose and at steady state. About the same variation was observed for AUC after a single 100 mg dose given as a rapidly dissolving tablet whereas at steady state the interindividual variation of AUC was only threefold (VII). Additional studies on single 50 mg doses on metoprolol have shown approximately the same spread between the peak plasma levels as in papers VI and VII (V, unpublished observations) and Ekelund et al. (to be published), whereas Haglund et al. (52) have reported a seventeenfold variation between the mean steady state plasma levels in 16 hypertensive patients treated with 100 mg of metoprolol tartrate t.i.d. for six weeks.

It has been shown in paper VI that the maximum concentration of metoprolol is significantly correlated to the elimination half-life so that subjects with the

lowest rate of elimination had the highest plasma concentrations of the drug. The differences between the peak plasma levels were, however, larger than between the elimination rates, probably due to differences in the first-pass effect.

Repeated administration of metoprolol on a b.i.d. or t.i.d. regimen gives rise to a slight cumulation of the drug in the body. In the hypertensive patients the peak plasma levels increased on average by about 45 per cent from the first dose to steady state. The increase was slightly higher, about 60 per cent, in the healthy subjects who were given 100 mg b.i.d. for four days (VII).

9. RELATIONSHIP BETWEEN DOSE AND EFFECT

Based on the classical receptor theory, it has been shown theoretically that the effect data can be fitted to a straight line in the 20—80 per cent effect region when doses are plotted on a logarithmic scale (47). A linear correlation between the effect on exercise heart rate and the logarithm of the dose has also been experimentally verified for several drugs including alprenolol and metoprolol (2, V). The data reported in these two studies indicate that the effect of 50 mg of orally administered metoprolol is about the same as for 100 mg of alprenolol and that the ratio between equipotent oral and intravenous doses of metoprolol is approximately 2.5:1. This value is consonant with the reported bioavailability of 40—50 per cent for orally administered metoprolol (IV, V).

10. RELATIONSHIP BETWEEN PLASMA LEVELS AND EFFECT

The rationale of correlating the pharmacological effect of a drug to the administered dose is based on the assumption that the intensity of the effect is dependent on the amount of drug in the body exclusive of that which may be unabsorbed in the gastrointestinal tract, in intramuscular depots etc. Very often, however, the content of drug in the body is poorly related to the given dose due to interindividual differences in, for instance, the first-pass effect or in the elimination capacity or due to poor absorption of the drug. For this kind of drug, including several beta-receptor antagonists and tricyclic antidepressants, the effect is better correlated to the plasma concentration of the drug than to the dose given. Thus, Alexanderson et al. (6) has reported a much better correlation between the effect of nortriptyline and the steady state plasma concentration than to dosage. A correlation between the plasma levels and the effect can only be expected, however, provided that the effect is rapidly reversible, implying that a given intensity of effect is associated with a particular drug

concentration at the receptor sites. In addition, the concentration of drug in the plasma should mirror the concentration of drug at the site of action. It is also important that the estimated effect variable is relevant for the pharmacological effect as otherwise no relationship to the plasma concentration can be expected (68).

Numerous studies on the beta-receptor antagonists have shown that inhibition of the increase of heart rate induced by exercise, glyceryl trinitrate, isoprenaline and tilting can be used as qualitative tests of beta-receptor blockade. The merits and drawbacks of the different methods have, for instance, been discussed by George et al. (44). In the studies included in this survey the beta-blocking action of alprenolol and metoprolol has been assessed by the reduction of exercise heart rate during submaximal exercise. The work load was individually adjusted to give a heart rate of about 150 beats per minutes in the control experiments. According to Robinson et al. (75), this heart rate is mainly an effect of an increased tone in the sympathetic nerve fibres while the withdrawal of vagal influence plays a relatively minor role. In addition to the exercise heart rate, the resting heart rate and the arterial blood pressure during exercise and at rest have been followed after metoprolol.

A. *Plasma levels and exercise heart rate*

The relationship between the effect on exercise tachycardia and the plasma concentration of alprenolol and metoprolol has been studied in healthy volunteers in papers III, V and VII. For both drugs the effect was linearly correlated to the logarithm of the plasma concentration of unchanged drug, both after intravenous and oral administration. Surprisingly small interindividual variations in the plasma levels of unchanged alprenolol associated with a certain degree of beta-blockade were obtained after oral administration in study III. The difference was only threefold whereas in another study by Åblad et al. (2) an almost one hundredfold variation has been reported.

The data presented in papers III and V indicate that after intravenous administration alprenolol and metoprolol induce on average about the same degree of beta-blockade at identical plasma levels. The relationship between the effect and the plasma concentration of unchanged drug differs, however, essentially after oral administration of the two beta-blockers. Thus, a certain degree of beta-blockade was associated with a two to three times lower plasma concentration after oral than after intravenous administration of alprenolol whereas intravenously and orally administered metoprolol induced approximately the same effect at identical plasma levels, i.e. the effect of a certain plasma concentration of metoprolol seems to be independent of the route of administration. The apparently greater potency of orally than of intravenously administered alprenolol at identical plasma levels has been shown to be due to the formation of the active metabolite 4-OH-alprenolol in quantities sufficient to influence significantly the beta-blockade after oral administration. A similar

discrepancy between the potency of orally and intravenously administered drug has also been reported for propranolol (30, 31). For this drug the relatively greater effect of the plasma concentrations of orally administered drug has been explained by the formation of 4-OH-propranolol, which, according to Fitzgerald and O'Donnell (41), is similar to propranolol in potency.

Linear relationships between the reduction of exercise heart rate and the logarithm of the plasma concentrations have also been reported for e.g. propranolol (31, 56), practolol (28, 83) and pindolol (9, 56). The experimental conditions in these studies differ, however, from the methods applied in the tests on alprenolol and metoprolol and the relative potency of the different beta-blockers, determined from the plasma levels of intravenously administered drug reducing the effect of potential active metabolites to a minimum, can therefore only be roughly estimated. Thus, propranolol seems to induce about the same beta-blockade as alprenolol and metoprolol at identical plasma levels after intravenous administration (56, III, V), which is in agreement with the 1:1 ratio of equipotent intravenous doses of propranolol and alprenolol reported by Johnsson et al. (58). Pindolol is, however, more potent than these compounds and equivalent degrees of beta-blockade were associated with five to tenfold lower plasma levels of pindolol than of propranolol (9, 56). On the other hand, practolol plasma levels in the μg range, i.e. substantially higher than for the other beta-blockers, are required to reduce the exercise heart rate (28). The difference between the plasma levels of the various beta-blockers associated with a certain degree of beta-blockade after intravenous administration mainly appears to be due to varying affinity to the beta-receptors.

B. *Plasma levels and resting heart rate*

The effect of metoprolol on the resting heart rate has been studied in two groups of healthy volunteers (V, VII) and in one group of patients with mild hypertension (VI). A significant reduction of the heart rate was obtained after 50 mg orally and 20 mg intravenously (V). The effect increased with the dose and after 100 mg orally the mean maximum reduction of the heart rate was about 8 beats per minute. A similar reduction of the resting heart rate was observed after the acute 100 mg dose in study VII. In the hypertensive patients the effect was linearly related to the plasma concentration of metoprolol and the relationship could be described by the same regression line as for the relationship between the effect on exercise heart rate and the plasma concentration in healthy subjects. The identical relationships might depend on a high tone in the sympathetic nervous system in the hypertensive patients. A similar relationship during resting conditions will not be observed for alprenolol due to its intrinsic activity.

C. *Effect on the arterial blood pressure*

Acutely administered beta-blockers have been found significantly to reduce the arterial systolic blood pressure during exercise in several studies (2, 59, 83, 85).

The decrease seems primarily to be due to a reduction in cardiac output which is linearly related to the drop in heart rate (48). In these studies, however, the investigators either have not found any correlation between the effect on the exercise systolic blood pressure and the plasma concentration (2, 85), or they have related the effect to the concentration on a linear scale which has led to a non-linear relationship (83). A linear and highly significant correlation between the reduction of the systolic blood pressure during exercise and the logarithm of the plasma concentration of unchanged drug was, however, obtained for metoprolol in healthy volunteers (VII). In this study a certain plasma concentration induced virtually identical per cent reduction in exercise heart rate and systolic blood pressure and the relationship between these effects and the logarithm of the plasma concentration could therefore be described by the same regression line. Due to the identical response of the effect variables to the plasma concentration of the drug, the effect on the exercise heart rate and on the systolic blood pressure declined at the same rate.

A more rapid return of the pressure to the control value and a less clear relationship between the effect on this variable and the plasma concentration than for the exercise heart rate was, however, reported in paper V. Similarly, Åblad et al. (2) have found that the dose of alprenolol is better correlated to its effect on exercise heart rate than to its effect on the systolic blood pressure. The reason for this is unknown but technical difficulties in recording the blood pressure during strenuous exercise might sometimes affect the precision of this variable. Furthermore, different groups of subjects might react differently in their homeostatic reflex mechanisms.

Single doses of metoprolol also decrease the resting systolic blood pressure. The effect was greater in patients with mild hypertension (VI) than in healthy volunteers (V, VII) but in none of the studies was the reduction of pressure significantly correlated to the logarithm of the plasma concentration. Possibly, a better relationship would have been obtained if the blood pressure had been recorded continuously instead of intermittently, as the resting systolic blood pressure fluctuates considerably from time to time.

D. *Duration of the beta-blockade*

Advances in the bioanalytical field during the last decade have greatly improved the possibilities of studying the concentration of drugs in various biological fluids and tissues, which has led to an enormous increase in the outflow of pharmacokinetic information about various drugs. Most of this information, however, has concerned the absorption, distribution and elimination of the compounds and the effect of various factors e.g. age and diseases, on these processes based on the realization that the effect is usually related to the plasma concentration of drug in some way. Only a limited number of studies have been directly focused on the kinetics of the pharmacological effect despite basic theories in this field already having been presented (42, 46, 47, 64, 88) and the fact that determination of the duration of the effect should be the most

important parameter for the choice of adequate dosage regimens. One reason for the small number of studies on the time course of the effect is the difficulties involved in developing quantitative methods for estimation of the effects of various drugs. Compared to many other types of drugs, the effect of the beta-blockers, however, can be determined with high accuracy by relatively simple methods, as previously discussed, and some beta-blockers therefore belong to the most well documented drugs in this respect.

The effect of alprenolol on exercise tachycardia has been shown to decline at a constant rate (zero-order kinetics) after both oral and intravenous administration (2, III). Similar time-effect relationships have also been obtained for metoprolol (V, VII) and for practolol (28), whereas the effect of propranolol on the chronotropic response to intravenously administered isoprenaline approximately paralleled the exponential decline of the plasma levels (70). The different type of kinetics of the effect of propranolol in this study might be due to the application of divergent methods for registration of the pharmacological effect.

The decline of the pharmacological effect at a constant rate follows from the exponential fall of the plasma concentration and the near-linear relationship between the effect and the logarithm of the plasma concentration (64) between 20 to 80 per cent of the maximum attainable effect. The rate of decline of the effect is equal to $m \times K_E / 2.303$ where m is the slope of the linear relationship between the effect and the logarithm of the plasma concentration and K_E is the first-order rate constant for the elimination of the drug. When m is known the rate of decline of the effect can consequently be used for determination of the elimination rate constant K_E and the half-life ($t_{1/2}$) of the drugs as $t_{1/2}$ is equal to $0.693/K_E$. This approach, being independent of the pharmacokinetic model after attainment of pseudo-distribution equilibrium between the concentration in the plasma and at the receptor sites, has given approximately the same half-life for alprenolol and metoprolol as determined from the terminal slope of the logarithm of the plasma concentration versus time curve.

As pointed out in papers V and VII, the constant rate of decline of the pharmacological activity implies a dose-dependent variation in the time for 50 per cent reduction of the maximum effect. This is for instance demonstrated in paper V by the finding that the maximum effect of an oral 20 mg dose was reduced to half of its initial value within 3.3 hours whereas the corresponding time for the 100 mg dose was 6.4 hours. For both doses the elimination half-life determined from the plasma data was three hours. A still longer duration of action was reported in study VII, where the maximum response to an oral 100 mg dose was reduced by 50 per cent during eight hours, indicating that about 25 per cent of the maximum attainable effect of this dose still remained in this panel of volunteers twelve hours after the administration of an acute dose. In this study, also, the time course of the effect on the systolic blood pressure during exercise was similar to that of the effect on the tachycardia, and a significant effect on the pressure persisted for more than twelve hours. The elimination half-life was in this study about four hours.

Studies in 14 patients with mild hypertension (VI) indicate that the effect of metoprolol on the resting heart rate and systolic blood pressure have about the same duration as the effect on the heart rate and systolic blood pressure in healthy subjects during exercise.

In study V on metoprolol, and in the study on alprenolol by Åblad et al. (2), the beta-blockade declined at the same constant rate at all dose levels tested from the time for the first effect registration and throughout the experiment. At sufficiently high doses, however, the effect will initially decline more slowly due to the non-linearity of the dose-response curve above 80 per cent of the maximum attainable effect. The time for attaining 50 per cent of the maximum effect might then deviate from the plasma half-life substantially more than reported above.

Little information is available about the duration of the effect of acute doses of other beta-receptor antagonists, but in a study by Carruthers et al. (27) the maximum effect of 400 mg of practolol was halved within 40—50 hours although the plasma half-life of this drug usually varies between ten and twelve hours. Thus, even for this drug the elimination half-life differs significantly from the time required to reduce the maximum response by 50 per cent. Accordingly, the *duration* of action of the beta-receptor antagonists cannot be determined exclusively from the plasma half-lives of these drugs but *effect data* are also required in order to enable an adequate estimation of the rate of decline of the pharmacological effect.

11. ACTIVE METABOLITES

Concurrent determinations of the plasma levels of the parent drug and the effect on exercise tachycardia have shown that the effect of orally administered alprenolol is to a significant extent due to the presence of the active metabolite 4-OH-alprenolol (III). The quantitative formation of this metabolite is associated with the route of administration and only minor amounts of the compound are recovered in the plasma after intravenous administration. In this respect alprenolol is similar to propranolol, which, according to Paterson et al. (70), only forms the active 4-OH-propranolol after oral administration. The time course of 4-OH-alprenolol in the body is, however, essentially different from that of 4-OH-propranolol. Data reported by, for example, Paterson et al. (70), Thompson et al. (86) and Cleveland and Shand (30) indicate that 4-OH-propranolol disappears more rapidly from the body than the parent drug, suggesting that the metabolite is formed chiefly during the initial transport from the gastrointestinal lumen into the systemic circulation. As regards 4-OH-alprenolol, the plasma levels of this metabolite decline at the same rate as for the parent drug as indicated by the apparently identical elimination half-lives after both oral and intravenous administration (III). The identical half-lives of

the two compounds, however, are due to continuing formation and rapid removal of the metabolite as long as alprenolol is recovered in the body. As mentioned previously, the half-life of the removal of intravenously administered 4-OH-alprenolol from the plasma was 0.3 hours, which is about ten times less than for the parent drug.

According to Fitzgerald and O'Donnell (41), identical plasma levels of propranolol and 4-OH-propranolol are equipotent with respect to beta-blockade in cats and similar findings have been reported for 4-OH-alprenolol by Carlsson (26).

Two active $beta_1$-receptor selective metabolites have been identified for metoprolol in the cat and the dog (21) but these metabolites are three to six times less potent than metoprolol. One of these compounds has also been recovered in the urine in man and might therefore to some extent contribute to the beta-blockade of metoprolol in man. It is evident, however, that no administration-route-dependent formation of any active metabolite of clinical importance exists for metoprolol as identical plasma levels of intravenously and orally administered drug induce the same degree of beta-blockade (V).

Little information about potentially active metabolites of the other beta-blockers is available. It seems, however, unlikely that such compounds should significantly contribute to the pharmacological activity of e.g. practolol and pindolol. The former drug is only metabolized to a slight extent (17, 40) and, according to Ohnhaus et al. (69), more than 90 per cent of the metabolites of pindolol in man are glucuronides and sulphates, which should be devoid of any beta-blocking activity.

12. SUMMARY

The pharmacokinetic and biopharmaceutical properties of the two adrenergic beta-receptor antagonists alprenolol and metoprolol have been reviewed on the basis of results presented in a number of recent investigations. In order to facilitate comparisons with other beta-blockers, relevant data from the literature concerning these compounds have been included.

Alprenolol and metoprolol are rapidly and completely absorbed from the alimentary tract but the first-pass effect of the liver reduces the bioavailability of orally administered drug to about 10 (alprenolol) and 50 per cent (metoprolol) respectively. The relatively low bioavailability of alprenolol is partly compensated for by the formation of the active metabolite 4-OH-alprenolol which significantly contributes to the beta-blocking effect after oral administration of alprenolol.

Both alprenolol and metoprolol are extensively distributed to extravascular sites. Pseudo-distribution equilibrium is generally attained within one hour after intravenous administration of the drugs.

The elimination half-life of alprenolol generally varies between two and three hours. Metoprolol is eliminated at a somewhat lower rate. Average half-lives of 3—4 hours have been obtained in four different studies. Only a minor fraction of the dose is excreted in unchanged form via the kidneys and more than 90 per cent of the dose is metabolized. Both compounds form active metabolites but only 4-OH-alprenolol — the major metabolite of alprenolol — has so far been reported to influence significantly the effect of the parent drug in man.

A linear correlation has been obtained between the beta-blockade and the logarithm of the plasma concentrations of alprenolol and metoprolol. Due to this relationship, the effect declines at a constant rate (zero-order kinetics). This type of kinetics implies that the duration of the beta-blockade cannot exclusively be determined from the plasma half-lives of alprenolol and metoprolol but effect data are also required to enable adequate estimation of the rate of decline of the pharmacological effect.

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ERRATA

Study I, page 60, last sentence, should read: "The solution was stirred at 40 rpm with a glass paddle (45 x 15 mm) located 3 cm above the bottom".

Study I, page 63, text to Table 2, should read: "Per cent of the dose recovered in the urine during 72 hours after the administration of four different tablet compositions".

Study I, page 66, second paragraph, line 2, should read: "level data is to apply the Wagner-Nelson equation (14) on the concentra-"

Study I, page 66, second paragraph, line 6, should read: "biotransformation in the series of the different preparations this method"

Study I, page 67, second paragraph, line 3, should read: "not possible to check if K_{el} remained unchanged in the series of sustained"

Study I, page 68, line 5, should read: "according to the overlapping parabols method (15). The mean values of"

Study VII, page 47, paragraph 6, line 6, should read: "and three of the slow-release preparations these data also represent the amount dissolved"

Study VII, page 55, paragraph 4, line 7, should read: "vitro data of the SR III tablet as previously obtained for alprenolol Durules®"